REMARKS

Applicants have canceled Claims 6-20 and 25 without disclaimer or prejudice, as being drawn to non-elected inventions. Applicants reserve the right to prosecute the subject matter of these claims in one or more continuation or divisional applications. Applicants also have withdrawn Claims 21-24, 26, and 28 as being drawn to non-elected process claims that are related to the currently pending product claims as process claims that otherwise include all the limitations of the currently pending product claims. Applicants also have canceled Claims 3 and 5; have amended Claims 1, 2, 4, 21-24, 26, and 27; and have added new Claims 29-32 herein. Enabling support for the amendments can be found in the application as filed, and therefore, no new matter is contained in the amendments and additions.

Applicants would like to thank Examiner Saoud for taking the time out of her schedule to discuss this case on October 31, 2006. Applicants agree with the substance of the Interview Summary mailed November 1, 2006. Examiner Saoud and Applicants' representative Kathryn Wade discussed Claims 1, 2, 4, and 27 with respect to the rejections made in the Office Action mailed July 11, 2006. In particular, proposed amendments to include a purity limitation were discussed with respect to avoiding the §§ 101, 102, and 103 rejections. In this regard, the Heymsfield et al. and Reagan et al. references were discussed. The breadth rejection of Claims 1 and 2 also was discussed, and proposed new claims reciting percent identity along with the function of the peptide also were discussed.

Reconsideration of the present application and allowance of resulting Claims 1, 2, 4, 27, and 29-32 are respectfully requested in view of the amendments and following remarks. Consideration and allowance of Claims 21-24, 26, and 28 are also respectfully requested.

I. Restriction Requirement

The Office Action made final the previous restriction requirement. Accordingly, Applicants have canceled Claims 6-20 and 25 as being directed to non-elected inventions. Applicants also have amended the currently pending claims to the extent that they refer to sequences other than the elected species. Applicants reserve the right to prosecute the subject

matter of these claims in one or more continuation or division applications.

Applicants also note that Claims 21-24, 26, and 28 are currently withdrawn, as being drawn to non-elected process claims that are related to the currently pending product claims as process claims that otherwise include all the limitations of the currently pending product claims. Applicants reserve the right to have these claims examined in the present application upon a determination that the currently pending product claims are allowable. Should the product claims not be found allowable, Applicants reserve the right to prosecute the subject matter of these withdrawn claims in one or more continuation or division applications.

II. Formalities Objections

A. Priority

The Office Action objected to the omission of the status of the applications to which this application claims priority. Applicants respectfully submit that the specification has been amended herein to include the status of each prior application. Therefore, Applicants respectfully request that the objections be withdrawn.

B. Abstract

The abstract was objected to as allegedly containing speculative applications not directed to the claimed invention. As requested, the abstract has been amended herein to refer only to the currently pending claims, which are directed to isolated anti-angiogenic peptides.

Applicants respectfully submit, however, that the claims that are currently withdrawn in this application are related to the currently pending product claims as process claims that otherwise include all the limitations of the currently pending product claims. According to MPEP § 821.04, the withdrawn process claims will be rejoined in this application when the product claims are found to be allowable. Therefore, upon the determination that the product claims are allowable, Applicants will amend the abstract to include a reference to the subject matter of the process claims.

B. Title of the Invention

The title was objected to as allegedly not being descriptive of the claimed invention. As requested, the title has been amended herein to refer only to the currently pending claims, which are directed to isolated anti-angiogenic peptides. As discussed above, however, Applicants respectfully submit that upon the determination that the product claims are allowable, Applicants will amend the title to include a reference to the subject matter of the process claims.

III. Rejections under 35 U.S.C. § 101

Claims 1-2 were rejected under 35 U.S.C. § 101, as allegedly being directed to non-statutory subject matter. In particular, the Office Action asserted that the claims do not include any limitations that would distinguish the claimed peptides from those which occur in nature. Applicants respectfully submit that the claims as amended are directed to statutory subject matter.

Applicants have amended the claims herein to reflect that the invention provides "isolated" antiangiogenic peptides. The specification defines the terms "isolated" and "substantially purified" as "a chemical composition which is essentially free of other cellular components" (page10, paragraph 55, lines 18-19).

Applicants respectfully submit that the present amendments to the claims render this rejection moot. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

IV. Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-2 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. In particular, the Office Action acknowledged that the specification is enabling for an isolated polypeptide having the amino acid sequence of SEQ ID NO:24, or an N-terminal fragment of growth hormone consisting of approximately 135 amino acids, but the Office Action asserted that the specification does not reasonably provide enablement for a genus

of anti-angiogenic peptides substantially identical to about 10-150 consecutive amino acids of human growth hormone.

Applicants respectfully submit that the claims as amended meet the requirements set forth in 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph with respect to the enablement requirement be withdrawn.

V. Rejections under 35 U.S.C. § 102(b)

Claims 1-2 and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by Heymsfield et al. (J. Clin. Invest. 60:563-570, 1977). In particular, the Office Action asserted that Heymsfield et al. teach human growth hormone that has been digested by plasmin, and pharmaceutical compositions of the N-terminal fragment. Applicants respectfully submit that Heymsfield et al. do not anticipate the present invention.

Applicants have amended the claims herein to reflect that the invention provides "isolated" antiangiogenic peptides. The specification defines the terms "isolated" and "substantially purified" as "a chemical composition which is essentially free of other cellular components" (page 10, paragraph 55, lines 18-19). The specification further states that "[a] protein which is the predominant species present in a preparation is substantially purified. Generally, a substantially purified or isolated protein will comprise more than 80% of all macromolecular species present in the preparation" (page 10, paragraph 55, lines 22-25). As Heymsfield et al. do not describe the separation of the plasmin-digested fragments from one another at all, the reference clearly does not disclose an isolated N-terminal fragment of growth hormone wherein the growth hormone accounts for 80% of the population of molecules in the composition, or pharmaceutical compositions of the same.

Applicants respectfully submit that the present amendments to the claims render moot these rejections. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be withdrawn.

VI. Rejections under 35 U.S.C. § 103(a)

Claims 1-2 and 4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Heymsfield et al. in light of Reagan et al., and further in view of Tokunaga et al. (Eur. J. Biochem. 153:445-449, 1985) and Mark et al. (U.S. Patent No. 4,959,314). In particular, the Office Action asserted that Heymsfield et al. teach that an N-terminal fragment of plasmin-digested human growth hormone has unique biological properties, and that Reagan et al. teach that the result of digestion of human growth hormone with plasmin is a 134 amino acid N-terminal fragment. The Office Action asserted that Tokunaga et al. teach human growth hormone which has been mutated at the cysteine residue at position 165 and that such a mutation renders the growth hormone more susceptible to plasmin hydrolysis than non-mutated growth hormone. The Office Action asserted that Mark et al. teach the general strategy of replacing Cys residues that are known not to be essential for biological function with other amino acids (particularly serine residues) to create "muteins" less likely to form intermolecular cross-links. The Office Action asserted that based on the cited art, it would have been obvious to one of ordinary skill in the art to make a 16 kDa N-terminal fragment of human growth hormone wherein the cysteine residue was modified to serine. Applicants respectfully submit that the present invention is not obvious over the cited references.

The Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. There must be a suggestion or motivation in the reference(s) to modify the reference(s); there must be a reasonable expectation of success; and the prior art reference(s) must teach all of the claim limitations. *See* MPEP § 2143. Here, the Patent Office has not met this burden because the prior art references do not teach all of the claim limitations. As discussed above, Heymsfield et al. do not describe the separation of the plasmin-digested fragments from one another, and therefore, the reference does not disclose an isolated N-terminal fragment of growth hormone or pharmaceutical compositions of the same that have antiangiogenic properties. Heymsfield et al. merely teach that plasmin digested S-carbamidomethylated human growth hormone retains certain biological properties of the intact human growth hormone, such as stimulating weight gain and cartilage metabolism in rats. None

of the remaining references cure this deficiency.

As is discussed in detail in the Declaration of Dr. Joseph Martial being submitted herewith, the N-terminal fragment of growth hormone is particularly difficult to separate from the smaller C-terminal fragment, and special efforts must be made to separate these fragments from one another. For this reason, because Reagan et al. did not take special efforts to separate the fragments, the N-terminal fragment cannot appear in a fraction eluted from the column described by Reagan et al. at a purity level where the N-terminal fragment is 80% or greater of the molecules in the fraction. Accordingly, Reagan et al. do not cure the deficiency in Heymsfield et al. Similarly, Tokunaga et al. do not cure this deficiency. Tokunaga et al. instead teach the introduction of an Ala residue at position 165 of growth hormone to prevent the disulfide bond between Cys-53 and Cys-165, making the protein more susceptible to plasmin cleavage. Tokunaga et al. do not teach the isolation of the N-terminal fragment of growth hormone. Moreover, Mark et al. do not cure this deficiency. Mark et al. teach the use of Ser residues for Cys residues to create proteins that are less likely to form intermolecular crosslinks.

For at least this reason, the Office Action failed to establish a *prima facie* case of obviousness, and the cited references do not teach or suggest the presently claimed invention. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

VII. Conclusion

Applicants believe that the present application, as amended, is now in condition for allowance. Favorable reconsideration of the application as amended and withdrawal of the objections are respectfully requested. The foregoing is submitted as a full and complete response to the Office Action mailed July 11, 2006.

A petition for a one month extension of time, as well as the appropriate fee, are being submitted herewith. No additional fees are believed to be due, however, the Commissioner is hereby authorized to charge any additional fees due or credit any overpayment to Deposit Account 19-5029 (Ref.: 18584-0015). If there are any issues that can be resolved by a telephone

conference or an Examiner's amendment, the Examiner is invited to call the undersigned attorney at (404) 853-8000.

Respectfully submitted,

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